



Adverse events of sugammadex that occurred in a Korean population

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Background: With increasing use, the incidence of adverse events associated with sugammadex, a neuromuscular blockade reverser, is increasing. This study aimed to identify and analyze cases of adverse events caused by sugammadex reported in Korean population.

Methods: Out of a total of 12 cases detected using various keywords in the Korean Journal of Anesthesia, Anesthesia and Pain Medicine (Seoul), KoreaMed, PubMed, EMBASE, Web of Science, and The Cochrane Library-CENTRAL from 2013 to December 2020, 10 cases directly associated with sugammadex were selected.

Results: Adverse events included five cases of anaphylaxis, one case of cardiac arrest, one case of profound bradycardia, one case of negative pressure pulmonary edema, and two cases of incomplete recovery. Three patients had American Society of Anesthesiologists physical status ≥ 3 , two had emergency surgery, and two had a history of allergic reaction. Neuromuscular monitoring was applied in nine cases. The average dose of sugammadex was 2.87 mg/kg, and there were six cases in which one full vial was used, regardless of the state of neuromuscular recovery. Sugammadex was administered immediately after surgery in two cases, at train of four (TOF) 0 in four cases, at TOF 3 in one case, and after evaluation of the clinical signs only with no neuromuscular monitoring in one case.

Conclusions: Even with neuromuscular monitoring, an excessive dose of sugammadex was observed. Given that adverse events tend to occur within 10 min of administration, continuous monitoring is important even after administration.

Keywords: Adverse effects; Anaphylaxis; Neuromuscular monitoring; Sugammadex.

INTRODUCTION

Sugammadex is a selective muscle relaxant-binding agent with a modified γ -cyclodextrin structure. This can effectively antagonize aminosteroidal non-depolarizing neuromuscular blocking agents. While anticholinesterase reaches the synaptic cleft and must bind to acetylcholinesterase, sugammadex rapidly encapsulates a free neuromuscular blocking

agent in the bloodstream without having to enter the synaptic cleft. After that, a concentration gradient is formed, and the neuromuscular blocking agent diffuses into the bloodstream at the receptor site, causing acetylcholine to recombine with the receptor. Due to the differences in these mechanisms, sugammadex exhibits a rapid onset of action [1]. In addition, sugammadex has no muscarinic effects, and neuromuscular blockade can be effectively reversed by adminis-

tration of an appropriate amount along with quantitative neuromuscular monitoring during a deep neuromuscular blockade.

In Korea, sugammadex was introduced in the market in 2013. Its clinical usage has gradually increased, with more than one million vials used by 2019. Although rare, several adverse events have been continuously reported.

Therefore, this study aimed to review all reported cases of adverse events associated with the use of sugammadex to date, that have been reported in Korean population, and to suggest a method to reduce adverse events based on the reported cases, as well as a literature review on this subject.

MATERIALS AND METHODS

Study design

This study was performed according to the recommendations of the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. The protocol was registered on PROSPERO (no. CRD42021286098, <https://www.crd.york.ac.uk/PROSPERO>).

Information sources and search strategy

Among the cases searched using the keywords “sugammadex”, “Bridion”, “Korea”, “anaphylaxis”, “allergic reaction”, “adverse event”, “adverse effect”, “side effect”, “complication” from January 2013 to December 2020 in *Korean Journal of Anesthesia, Anesthesia and Pain Medicine* (Seoul), KoreaMed, PubMed, EMBASE, Web of Science, and The Cochrane Library-CENTRAL those corresponding to the Korean population were selected. Medical Subject Heading (MeSH) terms were used.

Data collection process and extracted items

Two authors extracted data from the original articles, and another author independently confirmed all the extracted data. The collected information included the year of occurrence of adverse events, frequency of occurrence by type of adverse event, and the characteristics of patients, surgery, anesthesia, and adverse events. Patient characteristics included age, sex, height (cm), weight (kg), body mass index (kg/m^2), American Society of Anesthesiologists physical status, and allergic history. The surgical characteristics included the type of surgery and surgical time (min). Anesthetic

characteristics included the type of anesthesia and the use of a neuromuscular monitoring device. The characteristics of adverse events included the amount of rocuronium used (mg), amount of sugammadex used (mg), amount of sugammadex used per body weight (mg/kg), the time of sugammadex administration, onset time of an adverse event after sugammadex administration (min), and time duration from sugammadex administration to extubation (min).

Statistical analysis

We estimated the incidence of sugammadex-induced adverse events based on the frequency of use (corporate secret) and the number of reported cases. Categorical data are described as simple descriptions, numbers, median and percentages. As the incidence of side effects of sugammadex is less than 0.1%, there had been difficulties to secure the number of related cases. Since only 10 cases were reported during the period from January 2013 to December 2020, it was difficult to establish general statistical significance. But fortunately, the reporting efficiency of severe adverse drug reactions has been reported to be five times more than that of non-serious adverse events [2]. Most of the reported sugammadex-related adverse events were life threatening; therefore, we assumed that its reporting efficiency would have been higher than others.

RESULTS

Study selection

We initially retrieved 497 articles from *Korean Journal of Anesthesia, Anesthesia and Pain Medicine* (Seoul), KoreaMed, PubMed, EMBASE, Web of Science, and The Cochrane Library-CENTRAL. After adjusting for duplicates, 103 studies remained. Out of them, 91 studies were discarded after reviewing the title and abstracts for the following reasons: articles that reported irrelevant topics, were categorized as letter to editors and were not case reports. The full texts of the 12 remaining studies were reviewed in detail; 2 studies were excluded because side effects were not directly related with sugammadex: one was about the adverse event of remifentanyl, not sugammadex, and the other one was a delayed onset of action upon re-administration of rocuronium after sugammadex. Thus, 10 cases were finally included in this article (Fig. 1).

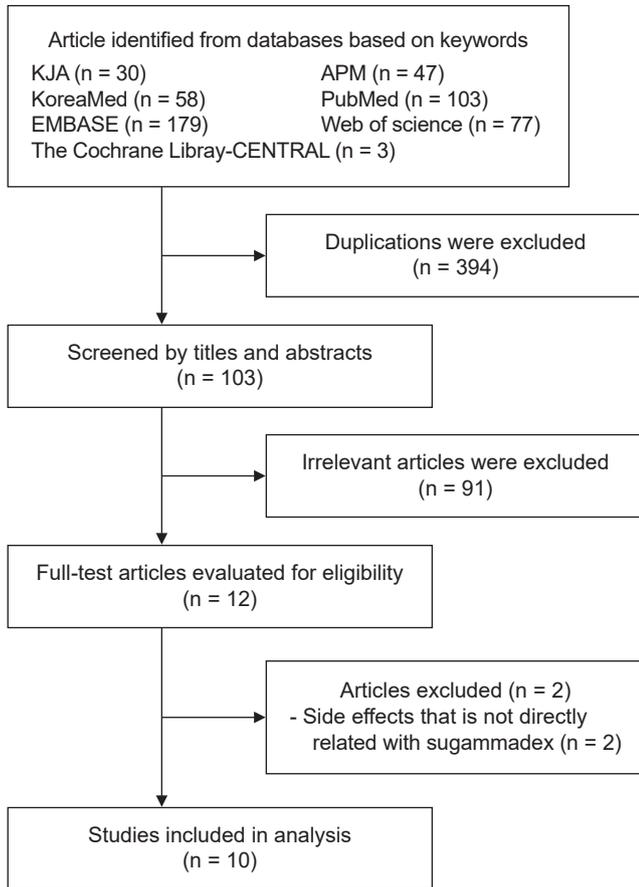


Fig. 1. PRISMA flow diagram. Flow diagram of search and study selection. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis, KJA: *Korean Journal of Anesthesia*; APM: *Anesthesia and Pain Medicine* (Seoul).

Characteristics of the included studies

The 10 cases of adverse events reported in Korea included 5 cases of anaphylaxis, 1 case of cardiac arrest, 1 case of profound bradycardia, 1 case of negative pressure pulmonary edema, and 2 cases of incomplete recovery (Fig. 2). The year or date of occurrence of adverse events was determined based on the publication year of the case reports, as exact years were not reported. There was one case in 2015, two cases in 2016, two cases in 2017, three cases in 2019, and two cases in 2020 (Table 1) [3-12].

In terms of patient, surgical, and anesthetic characteristics, there were three cases with American Society of Anesthesiologists physical status ≥ 3 , two cases with emergency surgery, two cases with allergic history (animal hair), and nine cases with neuromuscular monitoring (Tables 1 and 2). A skin prick test was performed in four of five anaphylaxis

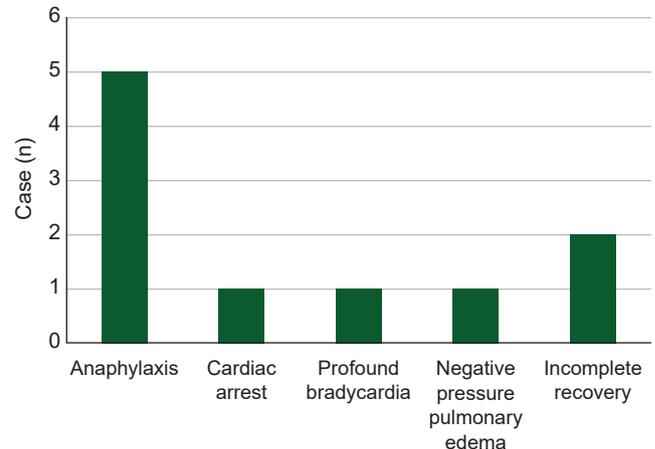


Fig. 2. Types of adverse events.

cases (patients 2 to 5) and a tryptase test was performed in one case (patient 3).

The average dose of sugammadex was 2.87 mg/kg, and there were six cases in which one full vial (200 mg) was used, regardless of the state of neuromuscular recovery. The administration time of sugammadex was immediately after the surgery in two cases, at train of four (TOF) 0 in four cases, at TOF 3 in one case, and after inspection of the clinical signs (handgrip, head lift, straight-leg raising, and tidal volume ≥ 8 ml/kg) without neuromuscular monitoring in one case (Tables 3 and 4).

The time between sugammadex administration and onset of adverse events was within 1 min in one case, 1-5 min in five cases, and 5-10 min in two cases (Tables 3 and 4).

After sugammadex administration, the extubation time was between 1-5 min in three cases, 5-10 min in one case, delayed more than 10 min due to incomplete recovery in two cases, 24 h after surgery in one case, and unknown in three cases (Tables 3 and 4). The case of incomplete recovery entailed underlying diseases, including amyotrophic lateral sclerosis and Duchenne muscular dystrophy.

DISCUSSION

The adverse events associated with sugammadex reported to date include hypersensitivity and anaphylaxis, cardiac arrest, profound bradycardia, incomplete reversal, negative pressure pulmonary edema, vomiting, dry mouth, tachycardia, hypotension, coagulopathy, interactions with steroids, and neuronal damage. These cases have also been reported in Korean populations; nevertheless, the incidence of or mortality due to adverse events has not been analyzed over

Table 1. Summary of Patient, Operation, Anesthesia by Patient Numbers

Patient	Side effect	Study	Age/Sex	Height (cm)/ Weight (kg)/ BMI (kg/m ²)	ASA physical status	Allergic history	Operation procedure	Operation time (min)	Anesthesia type	NIMM
1	Anaphylaxis	Hwang et al. 2015 [3]	69/F	158/50/20	2	None	Resection of varicose vein	60	Volatile (sevoflurane)	0
2		Koo et al. 2019 [4]	60/M	160/61/23.8	2E	None	Foreign body remove in eye	102	Volatile (desflurane)	0
3		Choi et al. 2020 [5]	60/M	159/64/25.3	2E	None	I & D, hand	40	Volatile (desflurane)	0
4		Kim et al. 2019 [6]	42/M	175/78/25.5	2	Animal hair	Endoscopic sinus surgery	55	Volatile (sevoflurane)	0
5		Yoo et al. 2016 [7]	35/M	182/109/32.9	2	Animal hair	Laparoscopic cholecystectomy	90	Volatile (sevoflurane)	0
6	Cardiac arrest	Ko et al. 2016 [8]	76/M	170/65/22.5	2	None	Robot-assisted radical prostatectomy	255	Volatile (desflurane)	0
7	Profound bradycardia	Choi et al. 2019 [9]	80/M	165/75/27.5	3	UKN	Laparoscopic cholecystectomy	180	TIVA	0
8	Negative pressure pulmonary edema	Lee et al. 2017 [10]	17/F	151/51/22.4	2	UKN	Lateral neck node dissection	250	Volatile (desflurane)	X
9	Incomplete recovery	Chun et al. 2020 [11]	71/M	UKN/54/UKN	3	UKN	Laparoscopic nephroureterectomy	220	Volatile (desflurane)	0
10		Kim and Chun 2017 [12]	11/M	UKN/53/UKN	3	UKN	Percutaneous nephrolithotomy	180	TIVA	0

BMI: body mass index, ASA: American Society of Anesthesiologists, NIMM: neuromuscular monitoring, UKN: unknown, TIVA: total intravenous anesthesia (propofol + remifentanyl).

Table 2. Characteristics of Patients, Operation, Anesthesia

Variable	Value
Patient characteristics	
Age (yr)	52.1 ± 24.57
Sex (M/F)	8/2
BMI (kg/m ²)	24.99 ± 3.94
ASA physical status	
1, 2	7
≥ 3	3
Allergy history	
	2
Operative characteristics	
Surgery time (min)	143.2 ± 83.26
Emergency surgery	2
Type of surgery	
Gastroenterology	2
Orthopedics	1
Neurosurgery	0
Urology	3
Gynecology	0
Otorhinolaryngology	2
Other	2
Anesthetic characteristics	
Type of anesthesia	
TIVA	2
Volatile anesthesia	8
Neuromuscular monitoring used	9

Values are presented as mean ± SD or number only. BMI: body mass index, ASA: American Society of Anesthesiologists, TIVA: total intravenous anesthesia.

the nine years of its clinical use in Korea. Based on the frequency of use and number of reported cases, the incidence of adverse events directly caused by sugammadex in Korea is approximately 0.0007%, and no cases of death caused by sugammadex have been reported to date. However, the actual number of cases are estimated to be higher than this. Potential explanations for this are that there may have been cases not analyzed for case reports. Additionally, cases may have been omitted because the causative drug is unclear. In addition, more than two vials may have been prescribed to one patient to reduce the incidence rate. However, even though the incidence rate is not yet high, certain adverse events can be fatal, and efforts are required to detect adverse events early and reduce the incidence rate.

The points of importance from the results include that there were three cases with American Society of Anesthesiologists physical status 3 and two cases with allergy history; sugammadex was administered immediately after surgery and at TOF 0 in several cases, even though neuromuscular

Table 3. Summary of Adverse Events by Patient Numbers

Patient	Rocuronium dose (mg)	Sugammadex dose (mg)	Sugammadex dose (mg)/Weight (kg)	Sugammadex administration time	Event onset time after sugammadex administration (min)	Extubation time after sugammadex administration (min)
1	40	100	2	TOF 2	8	3
2	50	200	3.28	End of surgery	2	UKN
3	40	200	3.13	End of surgery	3	UKN
4	50	200	2.56	TOF 0	< 10	5
5	90	200	1.83	TOF 3	2	2
6	100	130	2	TOF 2	2	Postoperative day 1
7	55	400	5.33	TOF 0	2	< 10
8	70	100	1.96	Confirming clinical signs*	Immediately	UKN
9	35	250	4.63	TOF 0	Delayed recovery	15.6
10	42	100	1.89	TOF 0	Delayed recovery	15

UKN: unknown, TOF: train of four. *Hand grip, head lift, straight-leg raising, tidal volume above 8 ml/kg.

Table 4. Characteristics of Adverse Events

Variable	Value
Average sugammadex dosage (mg/kg)	2.87 ± 1.23
Use of entire vial (200 mg) of sugammadex	6
Sugammadex administration time (min)	
End of surgery	2
TOF 0	4
TOF 2	2
TOF 3	1
Confirming clinical signs*	1
Adverse event onset time after sugammadex administration (min)	
Immediately (< 1 min)	1
1 < value ≤ 5	5
5 < value ≤ 10	2
No adverse events	2
Extubation time after sugammadex administration (min)	
1 < value ≤ 5	3
5 < value ≤ 10	1
> 10	2
Postoperative day 1	1
Unknown	3

Values are presented as mean ± SD or number only. TOF: train of four. *Hand grip, head lift, straight-leg raising, tidal volume above 8 ml/kg.

monitoring was performed in nine cases; an average of 2.87 mg/kg of sugammadex was administered even though 400 mg was administered in patient 7, and one full vial was used in 6 cases. Currently, 200 mg of sugammadex in one vial is used most commonly in clinical practice. Many practitioners tend to administer the entire 200 mg of sugammadex in one vial, as the remaining amount must be discarded. They also

tend to use one full vial to prevent residual neuromuscular block by administering a larger amount than necessary [13]. Of the six cases in which one full vial was used, the use of one vial in a patient weighing 109 kg at TOF 3 was considered appropriate; in three cases, the use of one full vial of sugammadex at TOF 0 was not considered incorrect, but appropriate in consideration of the risk of adverse events. In two cases, the dose of 3.28 mg/kg and 3.13 mg/kg, respectively, without inspection of the TOF after surgery despite TOF monitoring was considered inappropriate. In these two cases, anaphylaxis occurred.

Neuromuscular monitoring provides an easy and effective method to reduce the excessive use of sugammadex. The minimal dose of sugammadex recommended by the manufacturer is 2 mg/kg at a TOF of 2. However, it is sufficient to use less than 2 mg/kg of sugammadex for a TOF of 2 or higher [14]. Therefore, the authors of this study predicted that administering sugammadex appropriately according to the degree of neuromuscular function recovery through quantitative neuromuscular monitoring and avoiding habitual administration of one full vial could effectively reduce the incidence and severity of adverse events. In addition, this can prevent interference in the neuromuscular-blocking effect when re-administering a neuromuscular blocking agent, as reintubation is required after extubation [15].

The most frequent adverse event in this study was anaphylaxis. The main structure of sugammadex, γ -cyclodextrin, is widely used in everyday life as a solubilizer or stabilizer for food and cosmetics. For the average person, the amount of γ -cyclodextrin consumed per day is 4–8.8 g [16]. This may have resulted in sensitization, which caused hypersensitivity to sugammadex. Therefore, even a patient ex-

posed to sugammadex for the first time may exhibit hypersensitivity due to cross-reactivity. Given that two out of five patients with cases of anaphylaxis had a history of allergies, a history of allergy itself may also help predict the occurrence of anaphylaxis. Anaphylaxis for sugammadex is thought to be mostly associated with IgE-mediated hypersensitivity (type I hypersensitivity). Therefore, as a diagnostic test, a skin test such as intradermal testing and skin prick test, and a tryptase test that can determine the activation of mast cells may be helpful [17]. Recently, it has been found that hypersensitivity not related to sugammadex-specific IgE or IgG exists. There are reports that anaphylaxis is caused by sugammadex-rocuronium complex and sugammadex molecules together, and not by the sugammadex molecule itself [18]. Unlike that of other drugs, the hypersensitivity reaction to sugammadex is dose-related. According to Min et al., no anaphylaxis occurred in 151 patients administered 4 mg/kg, but one case of anaphylaxis occurred in 148 patients administered 16 mg/kg [19]. Anesthesiologists should always be aware that anaphylaxis may occur within 10 min of sugammadex administration, even in patients with no allergic history in the past, and the relationship with the dose should also be considered.

Sugammadex is known to cause a third-degree atrioventricular block, QT prolongation, and coronary vasospasm, leading to profound bradycardia and cardiac arrest [20]. Such complications occurred in healthy patients with no underlying cardiac diseases. In Korea, cardiac arrests have occurred in a patient with no underlying cardiac disease or symptoms other than atypical chest pain [8]. Importantly, the severity may increase in proportion to the dose, as the cardiovascular effect of sugammadex is associated with free sugammadex molecules [21]. Therefore, in all patients administered sugammadex, cardiovascular monitoring must be performed for at least 10 min after administration, with appropriate dosing of sugammadex.

Negative pressure pulmonary edema is thought to have occurred due to rapid recovery of respiratory force due to administration of sugammadex in the presence of upper airway collapsibility, such as laryngospasm [22]. When a large inspiratory force is applied in the state of obstruction in the upper airway, a large intrathoracic negative pressure is created to increase the blood flow to the pulmonary vasculature. As a result, pulmonary edema may occur due to an excessive increase in hydrostatic pressure and distension of the pulmonary vessel [23]. Even in this case, excessive use of sugammadex could be problematic. The reason for this is

that if laryngospasm is severe, it may be necessary to administer an additional neuromuscular blocker for reintubation [24]. At this time, free sugammadex molecules may interfere with neuromuscular blockade. Therefore, in this case, another type of neuromuscular blocking agent should be used. In addition, when excessive sugammadex is administered, T4 recovery is faster than expected, before T1 recovery, and the TOF ratio may increase, leading to errors in judgment [25]. From another point of view, negative pulmonary edema can also occur due to residual neuromuscular block. Inspiratory muscles, such as the diaphragm, are resistant to neuromuscular block agents and tend to be blocked less intensively or recover faster. Therefore, the onset and offset of neuromuscular blocking agents are more rapid [26]. Eikermann et al. reported that four patients displayed upper airway obstruction in the state of minimal residual neuromuscular block at a TOF ratio of 0.83 ± 0.06 . This is because inspiratory muscles are less susceptible to curarization than expiratory muscles [27]. Negative pulmonary edema is also predicted to occur because of such an imbalance. Therefore, anesthesiologists should keep in mind that negative pressure pulmonary edema can occur due to residual neuromuscular block as well as rapid recovery by sugammadex and should focus on maintaining airway patency.

In two cases of incomplete recovery, there were underlying neuromuscular diseases (amyotrophic lateral sclerosis and Duchenne muscular dystrophy). In both cases, sugammadex was administered at TOF 0, and the time to extubation after sugammadex administration was 15.6 min and 15 min, respectively. However, the presence of neuromuscular diseases does not necessarily cause delayed recovery [28], and although rare, delayed recovery may occur in healthy patients [29]. Since these patients may also experience additional adverse events due to excessive sugammadex, determining the appropriate dose of sugammadex through quantitative neuromuscular monitoring will help prevent adverse events.

This study has several limitations. First, as the number of cases was small due to difficulties in obtaining the data; therefore, there may have been insufficient power to detect statistical significance. However, even based on the cases reported so far, increased attention to the monitoring of neuromuscular function and patients' vital signs in conjunction with the use of sugammadex seems to be effective in reducing the incidence and severity of adverse events. Second, it was not known whether neuromuscular monitoring was performed after surgery. There was no mention of residual

paralysis in any of the ten cases. Since the authors of this study aimed to suggest the administration of sugammadex at an appropriate dose, such a suggestion may have been better supported if stability against residual paralysis was ensured by postoperative neuromuscular monitoring.

In conclusion, a review of the cases of adverse events directly caused by sugammadex in the Korean population shows that the incidence and severity of adverse events could be reduced through routine neuromuscular monitoring and careful administration of sugammadex [14]. In addition, sufficient recovery time as well as monitoring is required until extubation after administration [20]. Recently, sugammadex dose-ranging studies based on cost-saving strategies have been conducted. These studies commonly emphasize quantitative neuromuscular monitoring to prevent residual neuromuscular block [30]. A better guideline for sugammadex administration is required to contribute not only to cost-effectiveness but also to the reduction of adverse effects.

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None.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Conceptualization: Woong Han, Dong Ho Park, Chang Yeong Jeong, Hong Seuk Yang. Data curation: Woong Han, Dong Ho Park, Hong Seuk Yang. Formal analysis: Woong Han, Jong Min Lee, Dong Ho Park, Hong Seuk Yang. Methodology: Woong Han, Dong Ho Park, Chia An Lee, Chang Yeong Jeong, Hong Seuk Yang. Project administration: Woong Han, Chia An Lee, Chang Yeong Jeong, Hong Seuk Yang. Visualization: Woong Han, Chia An Lee, Chang Yeong Jeong, Hong Seuk Yang. Writing - original draft: Woong Han, Jong Min Lee. Writing - review & editing: Dong Ho Park,

Chia An Lee, Chang Yeong Jeong, Hong Seuk Yang. Investigation: Woong Han, Jong Min Lee, Chang Yeong Jeong, Hong Seuk Yang. Resources: Woong Han, Jong Min Lee, Dong Ho Park, Chang Yeong Jeong, Hong Seuk Yang. Supervision: Dong Ho Park, Chia An Lee, Chang Yeong Jeong, Hong Seuk Yang. Validation: Woong Han, Jong Min Lee, Dong Ho Park, Chang Yeong Jeong, Hong Seuk Yang.

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